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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,454	10/15/2001	Mark D. Erion	030727.0027.CON1	5123
29865	7590	08/29/2002	EXAMINER	
BROBECK, PHLEGER & HARRISON LLP 2390 EL CAMINO REAL SAN DIEGO, CA 92130			JONES, DAMERON LEVEST	
		ART UNIT	PAPER NUMBER	
		1616		
DATE MAILED: 08/29/2002				

Please find below and/or attached an Office communication concerning this application or proceeding.

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Brobeck, Phleger & Harrison LLP

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<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/978,454	ERION ET AL.
	Examiner D. L. Jones	Art Unit 1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) Responsive to communication(s) filed on 11/15/01; 1/25/02; and 2/8/02.

2a) This action is FINAL.                  2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4) Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
 If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
 a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.

4) Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.  
 5) Notice of Informal Patent Application (PTO-152)  
 6) Other:

## **ACKNOWLEDGMENTS**

1. The Examiner acknowledges receipt of the following:
  - a. Paper No. 2, filed 11/15/01, wherein claims 2-167 were canceled; and
  - b. Paper No. 3, filed 1/25/02, wherein claims 5 was amended and claim 13 was added. (Note: *It is duly noted that Applicant is attempting to amend and add claims that were canceled in the amendment filed 11/15/01, Paper No. 2.*)

Note: Claim 1 is pending.

## **APPLICANT'S INVENTION**

2. Applicant's invention is directed to a method of enhancing oral bioavailability of a parent drug by administering a compound of formula I as set forth in independent claim 1.

## **STATUTORY DOUBLE PATENTING**

3. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

4. Claim 1 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of prior U.S. Patent No. 6,312,662 B1. This is a double patenting rejection.

#### **ABSTRACT**

5. The abstract of the disclosure is objected to because it exceeds 25 lines of text. Correction is required. See MPEP § 608.01(b).

#### **SPECIFICATION**

6. The disclosure is objected to because of the following informalities: a portion of the structure is missing from page 52 (line 52) and page 54 (line 1).

Appropriate correction is required.

#### **CONTINUING DATA**

7. Applicant is respectfully requested to update the continuing data appearing on page 1, first paragraph, of the specification.

**COMMENTS/NOTES**

8. Applicant is respectfully suggested to insert the term 'containing' in claim 1, line 9, after the term 'optionally'.

9. It is noted that a prior art rejection has not been made over claim 1. Thus, claim 1 is allowable over the prior art; however, Applicant MUST address and overcome the double patenting rejection, update the continuing data, amend the abstract, and submit clean copies of the structures on pages 52 and 54. In particular, the claims are distinguished over the prior art of record because it neither anticipates nor renders obvious a method of enhancing oral bioavailability of a parent drug by administering a prodrug of formula I as set forth in independent claim 1.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose' Dees can be reached on (703) 308- 4628. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Art Unit: 1616

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.



D. L. Jones  
Primary Examiner  
Art Unit 1616

August 22, 2002

## NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

The drawing(s) filed (insert date) 10-15-01 are:

A.  approved by the Draftsperson under 37 CFR 1.84 or 1.152.  
 B.  objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawing must be submitted according to the instructions on the back of this notice.

**1. DRAWINGS.** 37 CFR 1.84(a): Acceptable categories of drawings:

Black ink. Color.  
 Color drawings are not acceptable until petition is granted.

Fig(s) \_\_\_\_\_  
 Pencil and non black ink not permitted. Fig(s) \_\_\_\_\_

**2. PHOTOGRAPHS.** 37 CFR 1.84(b)

1 full-tone set is required. Fig(s) \_\_\_\_\_  
 Photographs may not be mounted. 37 CFR 1.84(e)

Poor quality (half-tone). Fig(s) \_\_\_\_\_

**3. TYPE OF PAPER.** 37 CFR 1.84(e)

Paper not flexible, strong, white, and durable.  
 Fig(s) \_\_\_\_\_

Erasures, alterations, overwritings, interlineations, folds, copy machine marks not accepted. Fig(s) \_\_\_\_\_

Mylar, velum paper is not acceptable (too thin).  
 Fig(s) \_\_\_\_\_

**4. SIZE OF PAPER.** 37 CFR 1.84(f): Acceptable sizes:

21.0 cm by 29.7 cm (DIN size A4)  
 21.6 cm by 27.9 cm (8 1/2 x 11 inches)

All drawing sheets not the same size.  
 Sheet(s) \_\_\_\_\_

Drawings sheets not an acceptable size. Fig(s) \_\_\_\_\_

**5. MARGINS.** 37 CFR 1.84(g): Acceptable margins:

Top 2.5 cm Left 2.5cm Right 1.5 cm Bottom 1.0 cm  
 SIZE: A4 Size

Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm  
 SIZE: 8 1/2 x 11

Margins not acceptable. Fig(s) \_\_\_\_\_  
 Top (T) \_\_\_\_\_ Left (L) \_\_\_\_\_  
 Right (R) \_\_\_\_\_ Bottom (B) \_\_\_\_\_

**6. VIEWS.** 37 CFR 1.84(h)

REMINDER: Specification may require revision to correspond to drawing changes.

Partial views. 37 CFR 1.84(h)(2):

Brackets needed to show figure as one entity.  
 Fig(s) \_\_\_\_\_

Views not labeled separately or properly.  
 Fig(s) \_\_\_\_\_

Enlarged view not labeled separately or properly.  
 Fig(s) \_\_\_\_\_

**7. SECTIONAL VIEWS.** 37 CFR 1.84 (h)(3)

Hatching not indicated for sectional portions of an object.  
 Fig(s) \_\_\_\_\_

Sectional designation should be noted with Arabic or Roman numbers. Fig(s) \_\_\_\_\_

**8. ARRANGEMENT OF VIEWS.** 37 CFR 1.84(i)

Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) \_\_\_\_\_

**9. SCALE.** 37 CFR 1.84(k)

Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction.  
 Fig(s) \_\_\_\_\_

**10. CHARACTER OF LINES, NUMBERS, & LETTERS.**

37 CFR 1.84(l)

Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (poor line quality).

Fig(s) 1A 1B

**11. SHADING.** 37 CFR 1.84(m)

Solid black areas pale. Fig(s) \_\_\_\_\_

Solid black shading not permitted. Fig(s) \_\_\_\_\_

Shade lines, pale, rough and blurred. Fig(s) \_\_\_\_\_

**12. NUMBERS, LETTERS, & REFERENCE CHARACTERS.**

37 CFR 1.84(p)

Numbers and reference characters not plain and legible.

Fig(s) 1A 1B

Figure legends are poor. Fig(s) \_\_\_\_\_

Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(1)

Fig(s) \_\_\_\_\_

English alphabet not used. 37 CFR 1.84(p)(2)

Figs \_\_\_\_\_

Numbers, letters and reference characters must be at least .32 cm (1/8 inch) in height. 37 CFR 1.84(p)(3)

Fig(s) \_\_\_\_\_

**13. LEAD LINES.** 37 CFR 1.84(q)

Lead lines cross each other. Fig(s) \_\_\_\_\_

Lead lines missing. Fig(s) \_\_\_\_\_

**14. NUMBERING OF SHEETS OF DRAWINGS.** 37 CFR 1.84(t)

Sheets not numbered consecutively, and in Arabic numerals

beginning with number 1. Sheet(s) \_\_\_\_\_

**15. NUMBERING OF VIEWS.** 37 CFR 1.84(u)

Views not numbered consecutively, and in Arabic numerals,

beginning with number 1. Fig(s) \_\_\_\_\_

**16. CORRECTIONS.** 37 CFR 1.84(w)

Corrections not made from prior PTO-948 dated \_\_\_\_\_

**17. DESIGN DRAWINGS.** 37 CFR 1.152

Surface shading shown not appropriate. Fig(s) \_\_\_\_\_

Solid black shading not used for color contrast.

Fig(s) \_\_\_\_\_

**COMMENTS**

REVIEWER J. CHASE DATE 8-22-02 TELEPHONE NO. 703 305 8420

ATTACHMENT TO PAPER NO. \_\_\_\_\_

<b>Notice of References Cited</b>		Application/Control No.	Applicant(s)/Patent Under Reexamination ERION ET AL.	
		09/978,454	Examiner	Art Unit D. L. Jones 1616

**U.S. PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-6,312,662 B1	11-2001	Erion et al	424/9.1
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

**FOREIGN PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

**NON-PATENT DOCUMENTS**

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

\*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)  
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

## LIST OF PATENTS AND OTHER ITEMS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT

(Use several sheets if necessary)

ATTY. D	NO.	SERIAL NO.
030727	027.CON1	094978,454
APPLICANT:		
ERION		
FILING DATE:	GROUP:	
10/15/01	TBA 1616	

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## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE
<i>N</i>	AA	3,018,302 A	01.23.62	Bielefeld, et al.	—	—	
<i>P</i>	AB	5,658,889	08/19/97	GRUBER, et al.	514	43	12/14/94

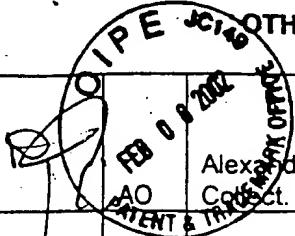
## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB CLASS	TRANSLAT. YES N
<i>T</i>	AC	91 19721 A1	12/26/91	WO	—	—	
	AD	98 39344 A	11/09/98	WO	—	—	
	AE	98 39343 A	11/09/98	WO	—	—	
	AF	98 39342 A	11/09/98	WO	—	—	
	AG	0 180 276 A1	05/07/86	EP	—	—	
	AH	3512781 A1	04/10/85	DE	—	—	
	AI	0 353 692 B1	07.02.90	EPO	—	—	
	AJ	WO 96/01267 A	18.01.96	WO	—	—	
	AK	0 161 955 A	21.11.85	EPO	—	—	
<i>V</i>	AL	WO 97/03679 A	06.02.97	WO	—	—	
<i>V</i>	AM	0 338 372 A	25.10.89	EPO	—	—	
<i>P</i>	AN	0 481 214 A	22.04.92	EPO	—	—	

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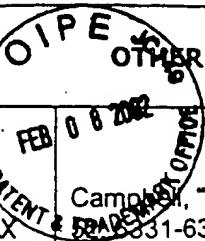
Alexander, et al., "Preparation of 9-(2- Phosphonomethoxyethyl) Adenine Esters as Potential Prodrugs," *Czech. Chem. Commun.*, 59: 1853-1869 (1994)COPY OF PAPERS  
ORIGINALLY FILEDAP Amin, et al., "1-Hydroxy-3-(methylpentylamino)-propylidene-1, 1-bisphosphonic Acid as a Potent Inhibitor of Squalene Synthase," *Arzneimittelforschung*, 46(8): 759-762 (1996)XA Atiq, O.T., et al., "Treatment of Unresectable Primary Liver cancer With Intrahepatic Fluorodeoxyuridine and Mitomycin C Through an Implantable Pump," *Cancer*, 69, 920-924 (1992)AQ Auberson, et al., "N-Phosphoalkyl-5-Aminomethylquinoxaline-2,3-Diones: *In Vivo* Active Ampa and NMDA(Glycine) Antagonists," *Bioorg. Med. Chem. Lett.*, 9: 249-254 (1999)AR Balthazor, et al. "Nickel-Catalyzed Arbuzov Reaction: Mechanistic Observation," *J. Org Chem.*, 45: 5425-5426 (1980)XB He, et al., "Inactivation of Cytochrome P450 3A4 by Bergamottin, a Component of Grapefruit Juice," *Chem. Res. Toxicol.* 1998, 11, 252-259AS Bespalov, et al., "Prologation of morphine analgesia by competitive NMDA receptor antagonist D-CPPene (SDZ EAA 494) in rats," *Eur. J. Pharmacol.* 351: 299-305 (1998)AT Bijsterbosch, et al., "Disposition of the acyclic Nucleoside Phosphonate (S)-9-(3-Hydroxy-2-Phosphonylmethoxypropyl) Adenine," *Antimicrobial Agents and Chemotherapy*, 42(5): 1146-1150 (1998)AU Bird, et al., "Synthesis of Novel N-Phosphonoalkyl Dipeptide Inhibitors of Human Collagenase," *J. Med. Chem.* 37: 158-169 (1994)AV Brill and Landon, et al., *Chem Rev.*, 84: 577-585 (1984)AW Campagne, et al. "Synthesis of Mixed Phosphate Diester Analogues of Dipeptides using BOP or PyBOP Reagents," *Tetrahedron Lett.*, 34(42): 6743-6744 (1993)

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ent Pages, etc.)

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AX	FEB 08 2002 CAMPBELL, "The Synthesis of Phosphonate Esters, an Extension of the Mitsunobu Reaction," <u>J Am Chem Soc</u> , 114(26): 531-6335 (1992)	TECH CENTER 2900/2900
AY	Casara, et al., "Synthesis of Acid Stable 5'-o-Fluorometer Phosphonates of Nucleosides," <u>Bioorg. Med. Chem. Lett.</u> , 2(2): 145-148 (1992)	COPY OF PAPERS ORIGINALLY FILED
AZ	Casteel, et al., "Steric and Electronic Effects in the Aryl Phosphate to Arylphoshonate Rearrangement," <u>Synthesis</u> , 691-693 (1991)	
XC	Chen, et al., "Sensitization of Human Breast Cancer Cels to Cyclophosphamide and Ifosfamide by Transfer of al Liver Cytochrome P450 Gene," <u>Cancer Research</u> , 56, 1331-1340 (1996)	
XD	Chen and Waxman "Intratumoral Activation and Enhanced Chemotherapeutic Effect of Oxazaphosphorines following Cytochrome P-450 Gene Transfer: Development of a Combined chemptherapy/Cancer Gene Therapy Strategy," <u>Cancer Research</u> , 55, 581-589 (1995)	
BA	De Lombaert, et al., "N-Phosphomethyl Dipeptides and Their Phosphonate Prodrugs, a New Generation of Neutral Endopeptidase (NEP, EC 3.4.24.11) Inhibitors" <u>J. Med. Chem</u> 37: 498-511 (1994)	
BB	De Lombaert, et al., "Pharmacological profile of a Non-Peptidic Dual Inhibitor of Neutral Endopeptidase 24.11 and Endothelin-converting enzyme," <u>Biochem Biophys Res Commun</u> 204: 407-412 (1994)	
BC	De Waziers, et al., "Cytochrome P 450 Isoenzymes, Epoxide Hydrolase and Glutathione Transferases in Rat and Human Hepatic and Extrahepatic Tissues," <u>J. Pharm. Exp. Ther.</u> 253: 387-394 (1990)	
BD	Dearfield, et al., "Analysis of the Genotoxicity of Nine Acrylate/Methacrylate Compounds in L5178Y Mouse Lymphoma Cells," <u>Mutagenesis</u> 4: 381-393 (1989)	
BE	Desos, et al., "Structure-Activity Relationships in a Series of 2(1H)-Quinolones Bearing Different Acidic Function in the 3-Position: 6,7-Dichloro-2(1H)-oxoquinoline-3-phosphonic Acid, a New Potent and Selectiv AMPA/Kainate Antagonist with Neuroprotective Properties," 39: 197-206 (1996)	
BF	Dickson, et al., "Orally Active Squalene Synthase Inhibitors: Bis((acyloxy)alkyl) Prodrugs of the $\alpha$ -Phosphonosulfonic Acid Moiety," <u>J. Med. Chem.</u> 39: 661-664 (1996)	

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## OTHER DOCUMENTS (Including Author, Title, Date)

PAGES, etc.)

<i>CAPE</i> 1 FEB 8 2002 PATENT & TRADEMARK OFFICE REVIEW	BG	Edmunson, et al., "Cyclic Organophosphorus Compounds. Part 23. Configurational Assignments in the 4-Phenyl-1,3,2λ5-dioxaphosphorinane Series. X-Ray Molecular Structure of cis-2-Benzylamino-4-phenyl-1,3,2-dioxaphosphorinane 2-Oxide," <i>J. Chem. Res. Synop.</i> , 5: 122-123 (1989)
	BI	Enriquez, et al., "Conjugation of Adenosine Arabinoside 5'-Monophosphate to Arabinogalactan: Synthesis, Characterization, and Antiviral Activity," <i>Bioconjugate Chem.</i> , 6: 195-202 (1995)
	BI	Farquhar, et al., "Biologically-Cleavable Phosphate Protective Groups: 4-Acetoxy-1,3,2-Dioxaphosphorinanes as Neutral Latent Precursors of Dianionic Phosphates," <i>Tetrahedron Lett.</i> , 36(5): 655-658 (1995)
	BJ	Farquhar, et al., "Biologically Reversible Phosphate-Protective Groups," <i>Journal of Pharmaceutical Sciences</i> 72(3): 324-325 (1983)
	BK	Farquhar, et al., "Synthesis and Biological Evaluation of 9-[5'-(2-Oxo-1,3,2-oxazaphosphorinan-2-yl)-β-D-arabinosyl]adenine and 9-[5'-(2-Oxo-1,3,2-dioxazaphosphorinan-2-yl)-β-D-arabinosyl]adenine: Potential Neutral Precursors of 9-[β-D-Arabinofuranosyl]adenine 5'-Monophosphate," <i>J. Med. Chem.</i> 28: 1358-1361 (1985)
	BL	Farquhar, et al., "Synthesis and Biological Evaluation of Neutral Derivatives of 5-Fluoro-2'-deoxyuridine 5'-Phosphate," <i>J. Med. Chem.</i> 26: 1153-1158 (1983)
	BM	Fiume, et al., "Inhibition of Hepatitis B Virus replication By Vidarabine Monophosphate Conjugated with Lactosaminated Serum Albumin," <i>The Lancet</i> 13-15 (1988)
	BN	Freed, et al., "Evidence for Acyloxymethyl Esters of Pyridimidene, 5'-Deoxyribonucleotides as extracellular sources of active α5'-deoxyribonucleotides in cultured cells," <i>Biochemical Pharmacology</i> , 38(19): 3193-3198 (1989)
	BO	Guida, et al., "Structure-Based Design of Inhibitors of Purine Nucleoside Phosphorylase. 4. A Study of Phosphate Mimics," <i>J. Med. Chem.</i> 37: 1109-1114 (1994)
	BP	Hirayama, et al., "Structure and conformation of a novel inhibitor of angiotensin I converting enzyme - a tripeptide containing phosphonic acid," <i>Int. J. Pept. Protein Res.</i> 38: 20-24 (1991)
	BQ	Hunston, et al., "Synthesis and Biological Properties of Some Cyclic Phosphotriesters Derived from 2'-Deoxy-5-fluorouridine," <i>J. Med. Chem.</i> 27: 440-444 (1984)

EXAMINER:

*D. Jones*

DATE CONSIDERED:

*8/21/02*

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## OTHER DOCUMENTS (Including Author, Title, Date)

Page, etc.)

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<i>D</i>	BR	Keenan, et al., "Pathology Reevaluation of the Kociba et al. (1978) Bioassay of 2,3,7,8-TCDD: Implications for Risk Assessment," <i>J. Tox. Envir. Health</i> 34: 279-296 (1991)
<i>O I P E 30/3/85</i> <i>FEB 08 2002</i> <i>PATENT &amp; TRADEMARK OFFICE</i>		Kelley, et al., "[[Guaninylalkyl] phosphinico] methyl] phosphonic Acids. Multisubstrate Analogue inhibitors of Human Erythrocyte Purine Nucleoside Phosphorylase," <i>J. Med. Chem.</i> 38: 1005-1014 (1995)
	BT	Khamnei and Torrence, "Neighboring Group Catalysis in the Design of Nucleotide Prodrugs," <i>J. Med. Chem.</i> 39: 4109-4115 (1996)
	BU	Kryuchkov, et al., <i>Izv. Akad. Nauk SSSR, Ser. Khim.</i> 6: 1201-1248 (1987)
	BV	Lok, et al., "Neurotoxicity associated with adenine arabinoside monophosphate in the treatment of chronic hepatitis B virus infection," <i>J. Antimicrob. Chemotherap.</i> 14: 93-99 (1984)
	BW	Lu et al., "Palladium-Catalyzed Reaction of Aryl Polyfluoroalkanesulfonates with O,O-Dialkyl Phosphonates" <i>Synthesis</i> , 726-727 (1987)
	BX	McGuigan, et al., "Kinase Bypass: A new strategy for Anti-Hiv Drug Design," <i>Bioorganic &amp; Medicinal Chemistry Letters</i> , 3(6): 1207-1210 (1993)
	BY	Meier, et al., "Cyclic Saligenyl Phosphotriesters of 2',3'-Dideoxy-2'3'-didehydrothymidine (d4t)," <i>Bioorganic &amp; Medicinal Chemistry Letters</i> , 7(2): 99-104 (1997)
	BZ	Meijer, et al., "Covalent and Noncovalent Protein Binding of Drugs: Implications for Hepatic Clearance, Storage, and Cell-Specific Drug Delivery," <i>Pharm. Res.</i> 6: 105-118 (1989)
<i>V</i>	CA	Melvin, "An Efficient Synthesis of 2-Hydroxyphenylphosphonates," <i>Tetrahedron Lett.</i> , 22(35): 3375-3376 (1981)
<i>P</i>	CB	Meyer, et al., "2"-O'-Acyl-6-thioinosine Cyclic 3', 5'-Phosphates as Prodrugs of Thioinosinic Acid," <i>J. Med. Chem.</i> 22: 811-815 (1979)

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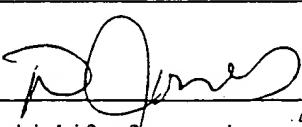
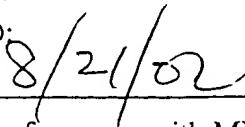
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RJ	CC	Mitchell, et al., "Bioreversible Protection for the Phospho Group: Bioactivation of the Di(4-acyloxybenzyl) and Mono(4-acyloxybenzyl) Phosphoesters of Methylphosphonate and Phosphonoacetate," <u>J. Chem. Soc. Perkin Trans. 1</u> 1992		
O I P E FEB 08 2002 PATENT & TRADEMARK OFFICE		Mitsunobu, "The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products," <u>Synthesis</u> , 1-28 (1981)		
		Moore, et al., "Comparison of Mutagenicity results for Nine Compounds evaluated at the <i>hprt</i> Locus in the Standard and Suspension CHO Assays," <u>Mutagenesis</u> 6: 77-85 (1991)		
	XE	Murray, et al., "Cytochrome P450 Expression is a common Molecular Event in Soft Tissue Sarcomas," <u>J. Pathology</u> , 171, 49-52 (1993)		
	XF	Murray, et al., "Cytochrome P450 CYP3A in human renal cell cancer," <u>British J. Cancer</u> , 79, 1836-1842 (1999)		
	CF	Neidlein, et al., "Mild Preparation of 1-Benzoyloxyiminoalkylphosphonic Dichlorides: Application to the Synthesis of Cyclic Phosphonic Diesters and Cyclic Monoester Amides," <u>Heterocycles</u> 35: 1185-1203 (1993)		
	CG	Nifantyev, et al., "Synthesis and Structure of Some Stable Phospholane-Phospholanes," <u>Phosphorus, Sulfur and Related Elements</u> 113: 1-13 (1996)		
	XG	Ogg, et al., <u>Xenobiotica</u> 29, 269-279 (1999)		
	CH	Ohashi, et al., "Synthesis of Phosphonosphingoglycolipid found in Marine Snail Turbo Cornutus," <u>Tetrahedron Lett.</u> , 29(10): 1189-1192 (1988)		
VJ	CI	Petrakis, et al., Palladium-Catalyzed Substitutions of Triflates Derived from Tyrosine-Containing Peptides and Simpler Hydroxyarenes Forming 4-(Diethoxyphosphoryl) phenylalanines and Diethyl Arylphosphonates," <u>J. Am. Chem. Soc.</u> , 109: 2831-2833 (1987)		
RJ	CJ	Redmore, "Phosphorus Derivatives of Nitrogen Heterocycles," <u>J. Org. Chem.</u> , 35(12): 4114-4117 (1970)		

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	CK	Shaw & Cundy, "Biological Screens of PMEA Prodrugs," <u>Pharm. Res.</u> 10 (supp) s24 (1993)		
CAPE FEB 8 2002 PATENT & TRADEMARK OFFICE	CL	Shih, et al., "Preparation and Structures of 2-Dimethylamino-4-phenyl-1,3,2-dioxaphosphorinane-2-oxides," <u>Bull. Inst. Chem. Acad. Sin.</u> 41: 9-16 (1994)		
		Turner, "A General Approach to the Synthesis of 1,6-,1,7-, and 1,8-Naphthyridines," <u>J. Org. Chem.</u> 55(15) (1990)		
	XH	Venook, A.P, "Treatment of Heptacellular Carcinoma: Too Many Options?" <u>J. Clin. Oncol.</u> 12, 1323-1334 (1994)		
	CN	Vo-Quang, et al., "(1-Amino-2-propenyl) Phosphonic Acid, an Inhibitor of Alanine Racemase and D-Alanine:D-Alanine Ligase," <u>J. Med. Chem.</u> 29(4): 579-581 (1986)		
	CO	Wagner, et al., "Direct Conversion of Tetrahydropyranylated Alcohols to the corresponding Bromides," <u>Tetrahedron Letters</u> 30(5): 557-558 (1989)		
	CP	Wallace, et al., "Design and Synthesis of Potent, Selective Inhibitors of Endothelin-Converting Enzyme," <u>J. Med. Chem.</u> 41: 1513-1523 (1998)		
	CQ	Walsh, et al., "The Structures of Grantianine and Scleratine," <u>J. Am. Chem. Soc.</u> , 78: 4455-4458 (1956)		
	XI	Watkins, et al., <u>Pharmacogenetics</u> 4, 171-184 (1994)		
	CR	Weibel, et al., "Potentiating Effect of {2-[2-[(2-Amino-1,6-Dihydro-6-oxo-9H-Purin-9-yl)Methyl]-Phenyl]Ethenyl}-Phosphonic Acid (MDL 74,428), A Potent Inhibitor of Purine Nucleoside Phosphorylase, and the Antiretroviral Activities of 2', 3'- Dideoxyinosine Combined to Ribavirin in Mice," <u>Biochem. Pharmacol.</u> 48(2):245-252 (1994)		
	CS	Wileman, et al., "Receptor - mediated endocytosis," <u>Biochem. J.</u> 232: 1-14 (1985)		

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XJ	Yu, et al., "In Vivo Modulation of alternative Pathways of P-450-Catalyzed Cyclophosphamide Metabolism: Impact on Pharmacokinetics and Antitumor Activity," <i>J. Pharm. Exp. Ther.</i> 288, 928-937 (1999)
CT	Zon, "Cyclophosphamide Analogues," <i>Progress in Med Chem.</i> 19: 1205-1246 (1982)
PATENT & TRADEMARK OFFICE	Predvoditelev D., et al., "Glycero-2-hydroxymethylene phosphates" <i>Journal of Organic Chemistry of the USSR</i> (English Translation) 13:1489-1492 (1977)
CV	Predvoditelev, D. et al., "Synthesis of lipids and their models on the basis of glycerol alkylene phosphites. V. Cyclic phosphatidylglycerol and phosphatidylhydroxyhomocholine" <i>Journal of Organic Chemistry of the USSR</i> (English Translation) 17:1156-1165 (1981)
CW	Hillers, et al., "Analogs of pyrimidinemono- and polynucleotides. VI. Phosphates of 1-(1,4-dihydroxy-2-pentyl) thymine and 1-(1,3-dihydroxy-2-propyl) uracil" 89 (17): 1-264 (1978)
CX	Farquhar, et al., "5'-4-(Pivaloyloxy)-1, 3, 2-dioxaphosphorinan -2-y]-2'-deoxy-5-fluorouridine: a membrane permeating prodrug of 5-fluoro-2'-deoxyuridylic acid (FDUMP)" <i>Journal of Medicinal Chemistry</i> 38:488-495 (1995)

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